# Instability and diffusion-driven blowup in some reaction-diffusion-ODE systems

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## 1 Introduction

We focus on systems of a single reaction-diffusion equation coupled with ordinary differential equations (we call such systems *reaction-diffusion-ODE systems*):

$$\boldsymbol{u}_t = \boldsymbol{f}(\boldsymbol{u}, v), \qquad \text{for} \qquad x \in \overline{\Omega},\ t > 0, \tag{1.1}$$

$$v_t = D\Delta v + g(\boldsymbol{u}, v), \qquad \text{for} \qquad x \in \Omega,\ t > 0, \tag{1.2}$$

where $\Omega \subset \mathbb{R}^N$ $(N \geq 1)$ is a bounded domain with smooth boundary $\partial\Omega$ and $D > 0$ is a constant which denotes a diffusion coefficient for $v$. The unknown functions $\boldsymbol{u} = \boldsymbol{u}(x, t)$ is given by a vector

$$\boldsymbol{u}(u, t) = \begin{pmatrix} u_1(x, t) \\ \vdots \\ u_n(x, t) \end{pmatrix}$$

and $v = v(x, t)$ is a scalar function. We impose the Neumann boundary condition on $v$:

$$\partial_\nu v = 0 \qquad \text{for} \quad x \in \partial\Omega,\ t > 0, \tag{1.3}$$

where $\partial_\nu = \partial/\partial\nu$ and $\nu$ is the outer unit normal to $\partial\Omega$, and initial data

$$\boldsymbol{u}(x, 0) = \boldsymbol{\varphi}(x) = \begin{pmatrix} \varphi_1(x) \\ \vdots \\ \varphi_n(x) \end{pmatrix}, \qquad v(x, 0) = \psi(x). \tag{1.4}$$

The nonlinearities $\boldsymbol{f} = \boldsymbol{f}(\boldsymbol{u}, v)$ and $g = g(\boldsymbol{u}, v)$ are arbitrary $C^2$-functions, where

$$\boldsymbol{f}(\boldsymbol{u}, v) = \begin{pmatrix} f_1(\boldsymbol{u}, v) \\ \vdots \\ f_n(\boldsymbol{u}, v) \end{pmatrix}.$$

Reaction-diffusion-ODE systems arise, for example, from modeling of interactions between cellular processes and diffusing growth factors. It was shown that receptor-ligand binding processes can be modeled by reaction-diffusion-ODE systems in the case when all membrane processes are homogeneous within the membrane (see [2]). We also find reaction-diffusion-ODE systems in ecological models (see [7]).

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We have studied a model based on receptor-ligand binding processes in [4], which is a model of early carcinogenesis proposed by A. Marciniak-Czochra and M. Kimmel:

$$u_t = \left(\frac{av}{u+v} - d_c\right)u, \qquad \text{for} \quad x \in [0,1], t > 0, \tag{1.5}$$

$$v_t = -d_b v + u^2 w - dv, \qquad \text{for} \quad x \in [0,1], t > 0, \tag{1.6}$$

$$w_t = \frac{1}{\gamma} w_{xx} - d_g w - u^2 w + dv + \kappa_0, \qquad \text{for} \quad x \in (0,1), t > 0, \tag{1.7}$$

where $a, d_c, d_b, d_g, d, \gamma, \kappa_0$ are positive constants. Here, $u(x,t)$, $v(x,t)$, $w(x,t)$ describe the densities of cells, bound and free growth factors, respectively. The binding processes of the free growth factor to the cell membrane activate the production of cell. We notice that all possible non-constant continuous positive stationary solutions of (1.5)–(1.7) can be constructed by phase portrait analysis when $\kappa_0$ and $\gamma$ are suitably large. For such stationary solutions, it was proved in [4] that they appear unstable.

In this paper, we would like to consider instability property of stationary solutions to general reaction-diffusion-ODE systems. In the next section, we state some known results for the simplest reaction-diffusion-ODE system, and general systems coupled with several ODEs will be studied in the last section.

## 2 The simplest system

The simplest reaction-diffusion-ODE system is the one which consists of a single reaction-diffusion equation coupled with an ordinary differential equation:

$$u_t = f(u,v), \qquad \text{for} \quad x \in \overline{\Omega},\ t > 0, \tag{2.1}$$

$$v_t = D\Delta v + g(u,v), \qquad \text{for} \quad x \in \Omega,\ t > 0, \tag{2.2}$$

$$\partial_\nu v = 0, \qquad \text{for} \quad x \in \partial\Omega. \tag{2.3}$$

Let $(U(x), V(x))$ be a stationary solution of (2.1)–(2.3). The stationary solution is called regular if there exists a solution of the equation $f(U(x), V(x)) = 0$ that is given by the relation $U(x) = k(V(x))$ for all $x \in \Omega$ with $C^2$-function $k = k(V)$. Then, every regular stationary solution $(U,V)$ satisfies the elliptic Neumann problem

$$D\Delta V + h(V) = 0, \qquad \text{for} \quad x \in \Omega, \tag{2.4}$$

$$\partial_\nu V = 0 \qquad \text{for} \quad x \in \partial\Omega, \tag{2.5}$$

where

$$h(V) = g(k(V), V) \qquad \text{and} \qquad U(x) = k(V(x)).$$

We note that each constant solution of (2.1)–(2.3) is a regular stationary solution. It was proved in [5] that all regular stationary solutions appear to be unstable under a simple assumption on the first equation of (2.1)–(2.3).

**Theorem 2.1** (Instability of regular solutions)**.** *Let* $(U, V)$ *be a regular stationary solutions of the problem* (2.1)–(2.3) *satisfying the following "autocatalysis condition":*

$$f_u(U(x_0), V(x_0)) > 0 \quad \textit{for some } x_0 \in \Omega.$$

*Then,* $(U, V)$ *is an unstable solution of the initial-boundary value problem* (2.1)–(2.3) *supplemented with nonnegative and continuous initial data.*

Concerning the dynamics, we have proved that space inhomogeneous solutions become unbounded (blowup) in either finite or infinite time, even if space homogeneous solutions are bounded uniformly in time ([1, 6, 3]). For example, we consider the following system with resource-consumer type nonlinearities:

$$u_t = -au + u^p\Phi(v), \qquad \text{for} \qquad x \in \overline{\Omega}, t > 0, \tag{2.6}$$
$$v_t = D\Delta v - bv - u^p\Phi(v) + \kappa, \qquad \text{for} \qquad x \in \Omega, t > 0, \tag{2.7}$$
$$\partial_\nu v = 0, \qquad \text{for} \qquad x \in \partial\Omega, t > 0, \tag{2.8}$$

where $D > 0$, $p > 1$, $a, b$ are positive constants and $\kappa \geq 0$. The function $\Phi \in C^3([0, \infty))$ satisfies that $\Phi(0) = 0$ and $\Phi(v) > 0$ for all $v > 0$.

Let $(U(x), V(x))$ be a positive stationary solution of (2.6)–(2.8). Since $U^{p-1} = a/\Phi(V)$,

$$f_u(U, V) = -a + pU^{p-1}\Phi(V) = a(p-1) > 0.$$

Thus, the assumption of Theorem 2.1 is satisfied and all regular stationary solutions of (2.6)–(2.8) are unstable.

We consider an initial-boundary value problem (2.6)–(2.8) supplemented with bounded, nonnegative and continuous initial data. When $D = 0$, it is easy to see that all nonnegative solutions to the problem exist for all $t > 0$ and bounded because we have

$$(u+v)_t \leq -\min\{a, b\}(u+v) + \kappa \qquad \text{for all} \quad t > 0.$$

On the other hand, in the case of $D > 0$, there are solutions which blow up in a finite time and at one point only. The following theorem states the result precisely.

**Theorem 2.2** (Blow up induced by diffusion)**.** *There exist* $\alpha \in (0, 1)$, $\varepsilon > 0$ *and* $R_0 > 0$ *such that if*

$$0 < u_0(x) < \left(u_0(0)^{1-p} + 2\varepsilon^{-(p-1)}|x|^\alpha\right)^{-\frac{1}{p-1}} \qquad \textit{for all} \quad x \in \Omega$$
$$u_0(0) \geq \left(\frac{a}{(1 - e^{(1-p)a})F_0}\right)^{\frac{1}{p-1}}, \qquad \textit{where} \quad F_0 = \inf_{v \geq R_0} f(v),$$
$$v_0(x) \equiv \bar{v}_0 > R_0 > 0, \qquad \textit{for all} \quad x \in \Omega,$$

*then the solution to the initial-boundary problem for the system* (2.6)–(2.8) *blows up at certain time* $T_{max} \leq 1$.

*Moreover, for all* $(x, t) \in \Omega \times [0, T_{max})$*, the solution satisfies*

$$0 < u(x, t) < \varepsilon|x|^{-\frac{\alpha}{p-1}} \quad \textit{and} \quad v(x, t) \geq R_0.$$

Our results on blowup shows that the following a priori estimate is not sufficient to prevent the blowup of solutions in a finite time: the total mass

$$\int_\Omega (u(x,t) + v(x,t))\ dx$$

of any nonnegative solution to the problem (2.6)–(2.8) does not blow up and $u(x,t)$ and $v(x,t)$ stay bound in $L^1(\Omega)$ uniformly in time.

## 2.1 Existence of regular stationary solutions

Let $(U(x), V(x))$ be a non-constant regular solution of the problem

$$f(u,v) = 0, \qquad \text{for} \qquad x \in \overline{\Omega},\ t > 0, \tag{2.9}$$

$$D\Delta v + g(u,v) = 0, \qquad \text{for} \qquad x \in \Omega,\ t > 0, \tag{2.10}$$

$$\partial_\nu v = 0, \qquad \text{for} \qquad x \in \partial\Omega. \tag{2.11}$$

As we mentioned before, it satisfies the elliptic Neumann problem (2.4)–(2.5). Since we impose the Neumann boundary condition, there exists $x_0 \in \Omega$ such that the vector $(\bar{u}, \bar{v}) \equiv (U(x_0), V(x_0))$ is a constant solution of (2.1)–(2.3). In such case, we say that a non-constant solution $(U, V)$ intersects a constant solution $(\bar{u}, \bar{v})$. Now, we have an important property of the constant solutions which are intersected by non-constant regular solutions. We call a constant solution satisfying the following conditions non-degenerate:

$$f_u(\bar{u},\bar{v}) + g_v(\bar{u},\bar{v}) \neq 0, \quad \det\begin{pmatrix} f_u(\bar{u},\bar{v}) & f_v(\bar{u},\bar{v}) \\ g_u(\bar{u},\bar{v}) & g_v(\bar{u},\bar{v}) \end{pmatrix} \neq 0 \quad \text{and} \quad f_u(\bar{u},\bar{v}) \neq 0. \tag{2.12}$$

**Proposition 2.1.** *Let $(U(x), V(x))$ be a non-constant regular stationary solution of (2.1)–(2.3). Then, there exists at least one constant solution $(\bar{u}, \bar{v})$ which is non-degenerate such that the following inequality holds:*

$$\frac{1}{f_u(\bar{u},\bar{v})} \det\begin{pmatrix} f_u(\bar{u},\bar{v}) & f_v(\bar{u},\bar{v}) \\ g_u(\bar{u},\bar{v}) & g_v(\bar{u},\bar{v}) \end{pmatrix} > 0. \tag{2.13}$$

This proposition is based on the property of solutions to a general elliptic Neumann problem (2.4)–(2.5).

**Lemma 2.1.** *Assume that $V \in C^2(\Omega) \cap C^1(\overline{\Omega})$ is a non-constant solution of the problem (2.4)–(2.5). Then, there exists $x_0 \in \overline{\Omega}$ and $a_0 \in \mathbb{R}$ such that*

$$V(x_0) = a_0, \quad h(a_0) = 0 \quad \textit{and} \quad h'(a_0) \geq 0.$$

Here, we note that

$$h'(\bar{v}) = \frac{1}{f_u(\bar{u},\bar{v})} \det\begin{pmatrix} f_u(\bar{u},\bar{v}) & f_v(\bar{u},\bar{v}) \\ g_u(\bar{u},\bar{v}) & g_v(\bar{u},\bar{v}) \end{pmatrix}.$$

By using Rabinowitz bifurcation theorem, at the constant solution $(\bar{u}, \bar{v})$ satisfying the inequality (2.13), there exists a sequence of diffusion coefficients $D_j \searrow 0$ such that the stationary problem corresponding to (2.1)–(2.3) has a nonconstant regular solutions.

# 3 The system coupled with several ODEs

The work of this section is a joint work with A. Marciniak-Czochra (University of Heidelberg), G. Karch (University of Wroclaw) and S. Cygan (University of Wroclaw).

We consider a stationary problem corresponding to (1.1)–(1.3):

$$\boldsymbol{f}(\boldsymbol{u}, v) = 0, \qquad \text{for} \quad x \in \overline{\Omega},\ t > 0, \tag{3.1}$$

$$D\Delta v + g(\boldsymbol{u}, v) = 0, \qquad \text{for} \quad x \in \Omega,\ t > 0, \tag{3.2}$$

$$\partial_\nu v = 0, \qquad \text{for} \quad x \in \partial\Omega,\ t > 0. \tag{3.3}$$

**Definition 3.1.** For $(\boldsymbol{U}, V) \in L^\infty(\Omega)^n \times W^{1,2}(\Omega)$, if the equation $\boldsymbol{f}(\boldsymbol{U}, V) = 0$ can be solved for almost all $x \in \Omega$ and if the equality

$$-\int_\Omega \nabla V(x) \cdot \nabla \eta(x)\, dx + \int_\Omega g(\boldsymbol{U}, V)\eta(x)\, dx = 0$$

holds true for all test function $\eta \in W^{1,2}(\Omega)$, then the $(\boldsymbol{U}, V)$ is called a weak solution of the problem (3.1)–(3.3).

**Definition 3.2** (Regular solutions)**.** First, we prepare some notation. Let $(\boldsymbol{U}, V) \in L^\infty(\Omega)^n \times W^{1,2}(\Omega)$ be a weak solution of (3.1)–(3.3). It is called regular if there exists a vector-valued function $\boldsymbol{k} \in C^2(\mathbb{R})$ such that

$$\boldsymbol{U}(x) = \boldsymbol{k}(V(x)) \qquad \text{for all} \quad x \in \Omega.$$

Similarly to the simplest case in Section 2, for every regular solution, the problem (3.1)–(3.3) becomes the elliptic Neumann problem

$$\Delta V + h(V) = 0 \quad \text{for} \quad x \in \Omega, \qquad \partial_\nu V = 0 \quad \text{for} \quad x \in \partial\Omega,$$

where $h(V) = g(\boldsymbol{k}(V), V)$.

Using the bifurcation theorem, we can show the existence of regular solutions of (3.1)–(3.3) under some assumptions. In this section, we do not discuss a detail of results on the existence.

## 3.1 Instability

For a linear operator $L$, $\sigma(L)$ denotes the spectrum of $L$. Moreover, we define

$$s(L) = \sup\{\mathrm{Re}(\lambda) \mid \lambda \in \sigma(L)\}.$$

For a given space $Y$, a vector $\boldsymbol{y} = (y_1, y_2, \dots y_n)^T \in Y^n$ means $y_j \in Y$ for each $1 \le j \le n$.

Let $(\boldsymbol{U}(x), V(x))$ be a bounded (not necessary regular) solution of the system (3.1)–(3.3). Substituting

$$\boldsymbol{u} = \boldsymbol{U} + \boldsymbol{\phi}, \qquad v = V + \psi,$$

into (1.1)–(1.2), we obtain a linear system for the perturbation $(\boldsymbol{\phi}, \psi)$ of the form:

$$\frac{\partial}{\partial t}\begin{pmatrix} \boldsymbol{\phi} \\ \psi \end{pmatrix} = \mathcal{L}\begin{pmatrix} \boldsymbol{\phi} \\ \psi \end{pmatrix} = \begin{pmatrix} 0 \\ D\Delta\phi \end{pmatrix} + \begin{pmatrix} \boldsymbol{f}_{\boldsymbol{u}}(\boldsymbol{U}, V) & \boldsymbol{f}_v(\boldsymbol{U}, V) \\ g_{\boldsymbol{u}}(\boldsymbol{U}, V) & g_v(\boldsymbol{U}, V) \end{pmatrix}\begin{pmatrix} \boldsymbol{\phi} \\ \psi \end{pmatrix} \tag{3.4}$$

with the Neumann boundary condition $\partial_\nu \phi = 0$. Here, $\mathcal{L}$ is an operator from $L^2(\Omega)^n \times W_N^{2,2}$ to $L^2(\Omega)^n \times L^2(\Omega)$, where

$$W_N^{2,2}(\Omega) = \{v \in W^{2,2}(\Omega) \mid \partial_\nu v = 0 \text{ on } \partial\Omega\}.$$

We will study the spectrum of the linearized operator $\mathcal{L}$ to see instability of solutions of (3.1)–(3.3). Actually, the following theorem holds:

**Theorem 3.1.** *If $\sigma(\mathcal{L}) > 0$, then $(\boldsymbol{U}, V)$ is an unstable of the initial-boundary value problem* (1.1)–(1.4).

As the result in Theorem 2.1, it is expected that the spectra of $\boldsymbol{f}_{\boldsymbol{u}}(\boldsymbol{U}, v)$ appears in the assumption of Theorem 3.1. In order to see this, we would like to see properties of the spectrum of $\mathcal{L}$. Here, $\boldsymbol{f}_{\boldsymbol{u}}(\boldsymbol{U}, v)$ is a $n \times n$ matrix given by

$$\boldsymbol{f}_{\boldsymbol{u}}(\boldsymbol{U}, v) = \begin{pmatrix} \frac{\partial f_1}{\partial u_1}(\boldsymbol{U}, V) & \cdots & \frac{\partial f_1}{\partial u_n}(\boldsymbol{U}, V) \\ \vdots & \ddots & \vdots \\ \frac{\partial f_n}{\partial u_1}(\boldsymbol{U}, V) & \cdots & \frac{\partial f_n}{\partial u_n}(\boldsymbol{U}, V) \end{pmatrix},$$

of which elements are $x$-dependent. In general, let $\boldsymbol{M}(x) = \{m_{j,k}(x)\}_{j,k=1}^n$ which is a $n \times n$ matrix with elements $m_{j,k} \in L^\infty(\Omega)$ define a multiplication operator

$$(\boldsymbol{M}(\cdot)\boldsymbol{u})(x) = \boldsymbol{M}(x)\boldsymbol{u}(x).$$

Then, we have

**Lemma 3.1.** *Assume that there exists $\Omega' \subset \Omega$ such that $m_{j,k}$ is continuous on $\Omega \setminus \Omega'$. Then,*

$$\sigma(\boldsymbol{M}(\cdot)) = \overline{\bigcup_{x \in \Omega\setminus\Omega'} \sigma(\boldsymbol{M}(x))}.$$

**Claim 3.1.**

$$\sigma(\boldsymbol{f}_{\boldsymbol{u}}(\cdot)) \subset \sigma(\mathcal{L}).$$

This claim follows from a similar procedure to that of Section 4.3 in [5]. Let $\lambda \in \sigma(\boldsymbol{f}_{\boldsymbol{u}}(\cdot))$. Suppose $(\mathcal{L} - \lambda \boldsymbol{I})^{-1}$ with $n \times n$ identity matrix $\boldsymbol{I}$ exists and bounded. Then, there exists $K > 0$ such that, for any $(\boldsymbol{\phi}, \psi) \in L^2(\Omega)^n \times W_N^{2,2}(\Omega)$, we obtain the following estimate

$$\begin{aligned} \|\boldsymbol{\phi}\|_{L^2(\Omega)^n} + \|\psi\|_{W^{2,2}(\Omega)} \le K\Big(&\|\boldsymbol{f}_{\boldsymbol{u}}(\cdot) - \lambda \boldsymbol{I})\boldsymbol{\phi} + \boldsymbol{f}_v(\cdot)\psi\|_{L^2(\Omega)^n} \\ &+ \|D\Delta\psi + g_{\boldsymbol{u}}(\cdot)\boldsymbol{\phi} + (g_v(\cdot) - \lambda)\psi\|_{L^2(\Omega)}\Big). \end{aligned}$$

From Lemma 3.1, there exists $x_0 \in \overline{\Omega}$ and a vector $\boldsymbol{\xi} \in \mathbb{R}^n$ with $\|\xi\| = 1$ such that $(\boldsymbol{f}_{\boldsymbol{u}}(x_0) - \lambda \boldsymbol{I})\boldsymbol{\xi} = 0$. Hence, for any $\varepsilon > 0$, there is a ball $B_\varepsilon \subset \Omega$ such that

$$\|(\boldsymbol{f}_{\boldsymbol{u}}(\cdot) - \lambda \boldsymbol{I})\boldsymbol{\xi}\|_{L^\infty(B_\varepsilon)} < \varepsilon.$$

For arbitrary $\psi \in C_c^\infty(\Omega)$ satisfying $\operatorname{supp}\psi \subset B_\varepsilon$, we can choose a function $\boldsymbol{\phi} = \boldsymbol{\xi} p \in L^2(\Omega)^n$ so that $\operatorname{supp}\boldsymbol{\phi} \subset B_\varepsilon$ and the following equation is satisfied:

$$D\Delta\psi + g_{\boldsymbol{u}}(\cdot)\boldsymbol{\phi} + (g_v(\cdot) - \lambda)\psi = \zeta,$$

where $\zeta \in L^2(\Omega)$ satisfies $\|\zeta\|_{L^2(\Omega)} \le \varepsilon \|\boldsymbol{\varphi}\|_{L^2(\Omega)^n}$. Therefore, we see that

$$\begin{aligned}
&\|\boldsymbol{\varphi}\|_{L^2(\Omega)^n} + \|\psi\|_{W^{2,2}(\Omega)} \\
&\quad \le K\Big(\|\boldsymbol{f}_{\boldsymbol{u}}(\cdot) - \lambda \boldsymbol{I})\boldsymbol{\varphi}\|_{L^2(\Omega)^n} + \|\boldsymbol{f}_v(\cdot)\psi\|_{L^2(\Omega)^n} + \|\zeta\|_{L^2(\Omega)}\Big) \\
&\quad \le K\Big(2\varepsilon\|\boldsymbol{\varphi}\|_{L^2(\Omega)^n} + \|\boldsymbol{f}_v(\cdot)\|_{L^\infty(\Omega)}\|\psi\|_{L^2(\Omega)}\Big).
\end{aligned}$$

This leads to the inequality

$$(1 - 2K\varepsilon)\|\boldsymbol{\varphi}\|_{L^2(\Omega)^n} + \|\psi\|_{W^{2,2}(\Omega)} \le \|\boldsymbol{f}_v(\cdot)\|_{L^\infty(\Omega)}\|\psi\|_{L^2(\Omega)},$$

which cannot hold true for all $\psi \in C_c^\infty(\Omega)$ with $\operatorname{supp}\psi \subset B_\varepsilon$.

If Claim 3.1 is obtained, then we can show that $\sigma(\mathcal{L})\backslash\sigma(\boldsymbol{f}_{\boldsymbol{u}}(\cdot))$ consists only of isolated points by the analytic Fredholm theorem. Hence, we see that the following lemma.

**Lemma 3.2.**

$$\sigma(\mathcal{L}) = \sigma(\boldsymbol{f}_{\boldsymbol{u}}(\cdot)) \cup \{\lambda \in \sigma(\mathcal{L}) \mid \lambda \textit{ is an eigenvalue of } \mathcal{L}\}.$$

We would like to have more information about an eigenvalue of $\mathcal{L}$. Let $\lambda \notin \sigma(\boldsymbol{f}_{\boldsymbol{u}}(\cdot))$. Then, the eigenvalue problem is

$$(\boldsymbol{f}_{\boldsymbol{u}}(\cdot) - \lambda \boldsymbol{I})\,\boldsymbol{\phi} + \boldsymbol{f}_v\psi = 0, \tag{3.5}$$

$$D\Delta\psi + g_{\boldsymbol{u}}(\cdot)\boldsymbol{\phi} + (g_v(\cdot) - \lambda)\,\psi = 0. \tag{3.6}$$

We can solve (3.5) with respect to $\boldsymbol{\phi}$ and substitute to (3.6) to obtain

$$D\Delta\psi + q(\lambda)\psi = 0, \qquad \partial_\nu\psi = 0, \tag{3.7}$$

where $q(\lambda) = -g_{\boldsymbol{u}}(\cdot)\,(\boldsymbol{f}_{\boldsymbol{u}}(\cdot) - \lambda \boldsymbol{I})^{-1}\,\boldsymbol{f}_v(\cdot) + g_v(\cdot) - \lambda$. We note that $q(\lambda)$ can be written in the form

$$q(\lambda) = \frac{1}{\det(\boldsymbol{f}_{\boldsymbol{u}}(\cdot) - \lambda \boldsymbol{I})}\det\begin{pmatrix} \boldsymbol{f}_{\boldsymbol{u}}(\cdot) - \lambda \boldsymbol{I} & \boldsymbol{f}_v(\cdot) \\ g_{\boldsymbol{u}}(\cdot) & g_v(\cdot) - \lambda \end{pmatrix}.$$

Hence, if $s(\mathcal{A}) > 0$, then there is a $\lambda$ with $\mathrm{Re}(\lambda) > 0$ such that the Neumann problem (3.7) has nontrivial solution $\psi$, where

$$\mathcal{A} = \begin{pmatrix} \boldsymbol{f}_{\boldsymbol{u}}(\boldsymbol{U}, V) & \boldsymbol{f}_v(\boldsymbol{U}, V) \\ g_{\boldsymbol{u}}(\boldsymbol{U}, V) & g_v(\boldsymbol{U}, V) \end{pmatrix}.$$

Consequently, we obtain the following assertion:

**Corollary 3.1.** *If*

$$s(\boldsymbol{f}_{\boldsymbol{u}}(\cdot)) > 0 \qquad \text{or} \qquad s(\mathcal{A}) > 0,$$

*then* $(\boldsymbol{U}, V)$ *is an unstable of the initial boundary value problem* (1.1)–(1.4).

Now, we consider a positive solution to the early carcinogenesis (1.5)–(1.7) in higher dimension:

$$\boldsymbol{u}_t = \begin{pmatrix} u_t \\ v_t \end{pmatrix} = \begin{pmatrix} \left(\dfrac{av}{u+v} - d_c\right) u \\ -d_b + u^2 w - dv \end{pmatrix} = \boldsymbol{f}(\boldsymbol{u}, w), \qquad \text{for} \qquad x \in \overline{\Omega},\ t > 0, \tag{3.8}$$

$$w_t = \frac{1}{\gamma}\Delta w - d_g w - u^2 w + dv + \kappa_0, \qquad \text{for} \qquad x \in \Omega,\ t > 0, \tag{3.9}$$

$$\partial_\nu w = 0, \qquad \text{for} \qquad x \in \partial\Omega,\ t > 0. \tag{3.10}$$

We assume that $a - d_c > 0$ because it is clear that $u$ has to be 0 for all $x \in \overline{\Omega}$ as $t \to \infty$ if $a < d_c$. Let $(\boldsymbol{U}(x), W(x)) = ((U(x), V(x)), W(x))$ be a bounded stationary solution with $\boldsymbol{U} \neq \boldsymbol{O}$. Then, it follows from the first equation $\boldsymbol{f}(\boldsymbol{U}, W) = 0$ that

$$U = \frac{a - d_c}{d_c} V, \qquad UW = \frac{d_c(d_b + d)}{a - d_c}.$$

Since the matrix $\boldsymbol{f}_{\boldsymbol{u}}(\cdot)$ becomes

$$\boldsymbol{f}_{\boldsymbol{u}}(\boldsymbol{U}, W) = \begin{pmatrix} -\dfrac{d_c(a-d_c)}{a} & \dfrac{(a-d_c)^2}{a} \\ \dfrac{2d_c(d_b+d)}{a-d_c} & -(d_b+d) \end{pmatrix},$$

an eigenvalue is a root of the following characteristic equation

$$\lambda^2 + \left(\frac{d_c(a-d_c)}{a} + d_b + d\right)\lambda - \frac{d_c(a-d_c)(d_b+d)}{a} = 0.$$

This equation has two roots, one is positive the other is negative. Therefore, we obtain that $s(\boldsymbol{f}_{\boldsymbol{u}}(\cdot)) > 0$ and see, from Theorem 3.1, that all stationary solutions of the problem (3.8)–(3.10) are unstable.

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